

Intensive care of patients with acute liver failure: Recommendations of the U.S. Acute Liver Failure Study Group

R. Todd Stravitz, MD; Andreas H. Kramer, MD, MSc; Timothy Davern, MD; A. Obaid S. Shaikh, MD; Stephen H. Caldwell, MD; Ravindra L. Mehta, MD; Andres T. Blei, MD; Robert J. Fontana, MD; Brendan M. McGuire, MD; Lorenzo Rossaro, MD; Alastair D. Smith, MD; William M. Lee, MD; the Acute Liver Failure Study Group

LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Define acute liver failure.
2. Explain management of acute liver failure.
3. Use this information in a clinical setting.

Dr. Shaikh has disclosed that he was/is on the speakers bureau for Schering Plough, Roche, Gilead Sciences, and Three Rivers Pharmaceuticals. Dr. Mehta has disclosed that he was/is the recipient of grant/research funds from Eli Lilly, was/is a consultant/advisor for Amgen, DSI, and Gambro, and was/is on the speakers bureau of Amgen. Dr. McGuire has disclosed that he is the recipient of grant/research funds from the National Institutes of Health. Dr. Lee has disclosed that he was/is the recipient of grant/research funds from Schering, Bristol-Myers, and Roche and was/is a consultant/advisor for AstraZeneca and Eli Lilly. All of the remaining authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

Lippincott CME Institute, Inc., has identified and resolved all faculty conflicts of interest regarding this educational activity.

Visit the *Critical Care Medicine* Web site (www.ccmjournal.org) for information on obtaining continuing medical education credit.

Objective: To provide a uniform platform from which to study acute liver failure, the U.S. Acute Liver Failure Study Group has sought to standardize the management of patients with acute liver failure within participating centers.

Methods: In areas where consensus could not be reached because of divergent practices and a paucity of studies in acute liver failure patients, additional information was gleaned from the intensive care literature and literature on the management of intracranial hypertension in non-acute liver failure patients. Experts in diverse fields were included in the development of a standard studywide management protocol.

Measurements and Main Results: Intracranial pressure monitoring is recommended in patients with advanced hepatic encephalopathy who are awaiting orthotopic liver transplantation. At an intracranial pressure of ≥ 25 mm Hg, osmotic therapy should be instituted with intravenous mannitol boluses. Patients with acute liver failure should be maintained in a mildly hyperosmotic state to minimize cerebral edema. Accordingly, serum sodium should be maintained at least within high normal limits, but hypertonic saline administered to 145–155 mmol/L may be considered in patients with intracranial hypertension refractory to mannitol.

Data are insufficient to recommend further therapy in patients who fail osmotherapy, although the induction of moderate hypothermia appears to be promising as a bridge to orthotopic liver transplantation. Empirical broad-spectrum antibiotics should be administered to any patient with acute liver failure who develops signs of the systemic inflammatory response syndrome, or unexplained progression to higher grades of encephalopathy. Other recommendations encompassing specific hematologic, renal, pulmonary, and endocrine complications of acute liver failure patients are provided, including their management during and after orthotopic liver transplantation.

Conclusions: The present consensus details the intensive care management of patients with acute liver failure. Such guidelines may be useful not only for the management of individual patients with acute liver failure, but also to improve the uniformity of practices across academic centers for the purpose of collaborative studies. (Crit Care Med 2007; 35:●●–●●)

KEY WORDS: acute liver failure; standardized care; intracranial pressure monitoring ; hepatic encephalopathy; orthotopic liver transplantation

Acute liver failure (ALF), defined as the onset of hepatic encephalopathy and coagulopathy within 26 wks of jaundice in a patient without preexisting liver disease, remains one of the most dramatic and highly mortal of all human afflictions. Nevertheless, the optimal management of patients with ALF remains very poorly defined and center-specific. Several reasons underlie the heterogeneous management of ALF, including the fact that ALF is a syndrome rather than a disease, representing the final manifestation of numerous etiologies. In addition, the syndrome is extremely difficult to study because of its high mortality and rarity (2000 U.S. cases per yr) (1).

The Adult U.S. Acute Liver Failure Study Group (ALFSG) was founded in 1997 to define the epidemiology and management of patients with ALF. Since its inception, the group has collected data on >1,100 patients with ALF from 23

prominent liver transplant centers. To more uniformly manage patients with ALF at participating centers, the ALFSG convened in December 2005 to review the available literature on the management of ALF, to compare the intensive care of patients with intracranial hypertension of various etiologies, and to compare practices within participating centers. Investigators in specialties outside of hepatology—including neuro-intensive care, nephrology, and coagulation—were invited to participate in formulating a standard studywide management protocol. Where possible, the protocol was based upon literature pertaining to patients with ALF; where studies specifically examining ALF did not exist, management recommendations were derived from other literature. Recommended measures were defined as those in which evidence-based studies suggest possible benefit in the clinical course or outcome of patients with ALF. Measures without supporting clinical data, but which potentially may be of benefit based upon a reasonable rationale, or supported by literature not specifically pertaining to patients with ALF, were deemed insufficient data to recommend. Finally, measures which clinical studies suggest may be detrimental were not recommended. The protocol was approved by the 23 member sites on September 23, 2006, and revisions were approved on May 10, 2007.

The present protocol expounds on a previous position paper (2) sanctioned by the American Association for the Study of Liver Diseases. The position paper offers general guidelines targeted at nonintensivists, and is cited within the present protocol for completeness and to avoid duplication of publication.

GENERAL MANAGEMENT

Patients with evidence of acute liver injury should be admitted to the hospital when accompanied by significant hepatocellular insufficiency (e.g., international normalized ratio >1.5). Because neurologic deterioration may be very rapid, patients should be moved to an intensive care unit at the onset of hepatic encephalopathy, and a discussion should ensue between the referring physician and intensivists at the nearest liver transplant center regarding timely transfer after stabilization. Such discussion should include whether endotracheal intubation should be performed be-

fore transfer. To establish a diagnosis, estimate disease severity, and predict the need for orthotopic liver transplantation (OLT), a battery of initial tests should be performed on arrival at the transplant center (2).

Etiology-Specific Treatments. Specific treatments (antidotes) for ALF have been systematically studied only for acetaminophen overdose. *N*-acetylcysteine (NAC) administration is recommended even if there is doubt concerning the timing, dose ingested, or plasma concentration of acetaminophen, and should not be withheld even if the ingestion was 48–72 hrs before presentation (3). Oral NAC is recommended as first-line therapy only in patients with mild (grade 1) hepatic encephalopathy; intravenous NAC should be administered to patients with >grade 1 encephalopathy, hypotension, or other reason that oral dosing might not be tolerated (e.g., vomiting, compromised airway, postoperative state, ileus). Doses for oral NAC administration should include a 140 mg/kg loading dose, followed by 70 mg/kg every 4 hrs. Doses for intravenous NAC administration vary according to protocol; one suggested schedule includes a 150 mg/kg load for 15–60 mins (usually in 5% dextrose, but any crystalloid is acceptable), followed by a maintenance infusion (e.g., 12.5 mg/kg per hr for 4 hrs, then 6.25 mg/kg per hr). NAC administration is recommended until there is firm evidence of improved hepatic function (resolution of hepatic encephalopathy, improving coagulopathy [international normalized ratio <1.5], and declining transaminases). The length of NAC administration should be determined by clinical improvement or outcome (death or liver transplant) rather than by time or serum acetaminophen levels; it should be emphasized that this period of time may extend well beyond 72–96 hrs.

Except for women with acute fatty liver of pregnancy or the hemolysis-elevated liver enzymes–low platelet syndrome, in whom prompt delivery of the fetus readily reverses ALF (4), there are generally insufficient data to recommend specific therapies for ALF due to other etiologies. However, etiology-specific measures are recommended by the ALFSG based upon anecdotal experience, relative innocuousness of the measures, and the high mortality of the clinical syndrome (Table 1) (2).

Associate Professor of Medicine, Section of Hepatology, Virginia Commonwealth University, Richmond, VA (RTS); Assistant Clinical Professor, Departments of Critical Care Medicine and Clinical Neurosciences, Foothills Medical Center, University of Calgary, Calgary, Canada (AHK); Associate Professor of Medicine, Department of Medicine/Gastroenterology, UCSF Liver Transplant Program, University of California at San Francisco, San Francisco, CA (TD); Associate Professor of Medicine, Center for Liver Diseases, University of Pittsburgh, Pittsburgh, PA (AOSS); Division of Gastroenterology and Hepatology, University of Virginia, Charlottesville, VA (SHC); Professor of Clinical Medicine, Associate Chair, Clinical Affairs, Department of Medicine, University of California at San Diego, San Diego, CA (RLM); Professor of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL (ATB); Associate Professor of Medicine, Medical Director, Liver Transplantation, Department of Medicine, University of Michigan Medical Center, Ann Arbor, MI (RJJ); JOB TITLE, Department of Medicine, University of Alabama, Birmingham, AL (BMM); Chief, Gastroenterology and Hepatology, Professor of Clinical Medicine, University of California at Davis, Sacramento, CA (LR); Assistant professor of Medicine, Department of Gastroenterology, Duke University Medical Center, Durham, NC (ADS); Professor of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX (WML).

Supported, in part, by National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases grant DK058369 (ALFSG, with WML as principal investigator).

Current address for Dr. Kramer: Departments of Critical Care Medicine and Clinical Neurosciences, Foothills Medical Center, University of Calgary, Calgary, AB, Canada.

For information regarding this article, E-mail: rstravit@hsc.vcu.edu

Copyright © 2007 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/01.CCM.0000287592.94554.5F

Table 1. Etiology-specific therapy of patients with ALF

Etiology	Therapy	References
APAP	NAC oral: 140 mg/kg load, then 70 mg/kg every 4 hrs NAC IV: 150 mg/kg load, then 12.5 mg/kg hourly × 4 hrs, then 6.25 mg/kg hourly	Dr. Smilkstein and colleagues (5) Dr. Buckley and colleagues (6), Dr. Smilkstein and colleagues (7)
<i>Amanita</i>	Penicillin G: 1 g/kg daily IV and NAC (as for APAP overdose)	Dr. Floersheim and colleagues (8), Dr. Broussard and colleagues (9)
HSV	Acyclovir: 30 mg/kg daily IV	Dr. Peters and colleagues (10)
AIH	Methylprednisolone 60 mg/day IV	Dr. Kessler and colleagues (11)
HBV	Lamivudine 100–150 mg/daily orally	Dr. Tillmann and colleagues (12)
AFLP/HELLP	Delivery of fetus	Dr. Mabie (4), Dr. Castro and colleagues (13)

APAP, acetaminophen; NAC, *N*-acetylcysteine; IV, intravenously; *Amanita*, mushroom intoxication; HSV, herpes simplex virus; AIH, autoimmune hepatitis; HBV, hepatitis B virus; AFLP/HELLP, acute fatty liver of pregnancy/hemolysis-elevated liver enzymes-low platelet syndrome.

MANAGEMENT OF COMPLICATIONS OF ALF

Hepatic Encephalopathy and Hyperammonemia. Ammonia, synthesized predominantly by gut microorganisms, is detoxified in astrocytes to osmotically active glutamine, thus contributing to the pathogenesis of hepatic encephalopathy and cerebral edema (14). The two standard treatments for hyperammonemia in patients with chronic liver disease are lactulose and nonabsorbable oral antibiotics. Currently, there are insufficient data to recommend the use of lactulose in patients with ALF. No effect on outcome was observed in one nonrandomized, retrospective series (published in abstract form only), although survival without liver transplant may have been increased (15). However, if lactulose is administered, the following precautions should be observed (1): Abdominal distention should be assessed at regular intervals, as lactulose may increase gaseous distention of the bowel, obscure the operative field during OLT, or may rarely precipitate megacolon (2, 16); lactulose by mouth or naso-gastric tube should not be administered to patients with late stages of hepatic encephalopathy without prior endotracheal intubation, considering the risk of aspiration (3); and the dose of lactulose should be titrated to avoid intravascular depletion (17). There are also insufficient data to support the use of nonabsorbable antibiotics (e.g., rifaximin, neomycin) to treat hepatic encephalopathy in patients with ALF. Neomycin is specifically not recommended because of the risk of nephrotoxicity (18).

Infection Prophylaxis and Surveillance. Infection remains one of the principal causes of death in patients with ALF and may be subtle in clinical presentation (19). The most common site of bacterial infection is the lung, followed by urinary

tract and blood, and the most commonly isolated organisms are Gram-positive cocci (*Staphylococci*, *Streptococci*) and enteric Gram-negative bacilli (20). Fungal infections, particularly *Candida*, may be present in one third of patients with ALF (21). Intravenous catheter-related sepsis represents a major source of avoidable infectious complications in patients with ALF (22); consequently, unnecessary intravenous catheters are to be avoided. Prophylactic parenteral and enteral antimicrobial regimens have not been shown to improve outcome or survival in patients with ALF, although key studies may have been underpowered (23). Therefore, there are insufficient data to recommend the routine use of antibiotic prophylaxis in all patients with ALF, particularly those with early stage hepatic encephalopathy. Although randomized studies exploring the use of daily bacterial surveillance cultures (blood and urine) and chest radiographs do not exist, such studies are recommended on the basis that patients with ALF frequently do not exhibit signs of infection, and early diagnosis of infection may improve outcome (20, 23). Empirical administration of antibiotics is recommended in the following circumstances where infection or the likelihood of impending sepsis is high: a) surveillance cultures reveal significant isolates (19); b) progression of, or advanced stage (III/IV), hepatic encephalopathy (22); c) refractory hypotension; or d) presence of systemic inflammatory response syndrome components (temperature >38 or <36°C, white blood count >12,000 or <4,000/mm³, pulse >90 beats/min) (24). Empirical antibiotics (antibacterial and antifungal agents) also are recommended for patients listed for OLT, because developing infection often results in delisting and immunosuppression is imminent, acknowledging that

specific data to support this practice do not exist. It should be recognized that the risk of developing infection with resistant organisms will increase with longer waiting times.

There are insufficient data to recommend specific antimicrobial agents for the indications above. However, broad-spectrum coverage for Gram-positive and Gram-negative bacteria, such as with a third-generation cephalosporin, should be chosen with consideration of patient-specific isolates from surveillance cultures, as well as historical hospital-specific isolates. Vancomycin is specifically recommended in all patients with possible intravenous catheter-related sepsis and/or risk factors for infection with methicillin-resistant *Staphylococcus aureus*. An antifungal agent also is recommended in any patient without prompt improvement in signs of infection after institution of antibacterial agents. Aminoglycosides are not recommended on the basis of risk of nephrotoxicity.

Sedation and Analgesia. Psychomotor agitation frequently contributes to intracranial hypertension in patients with ALF, especially as patients progress to stage III/IV hepatic encephalopathy (25). Pain also may increase intracranial pressure (26). Therefore, adequate analgesia and judicious sedation is required in patients who progress to stage III/IV hepatic encephalopathy, particularly before placement of invasive devices, such as intracranial pressure monitors or endotracheal tubes.

There are insufficient data to recommend a standard agent for sedation in patients with ALF. However, it should be recognized that both propofol and benzodiazepines, the most commonly used sedatives, increase γ -aminobutyric acid-ergic neurotransmission, and therefore may exacerbate hepatic encephalopathy

(27, 28). Although the metabolism of all agents used for sedation is attenuated in patients with ALF, the recovery time from propofol is shorter than from benzodiazepines, which may allow more reliable neurologic examination when the infusion is temporarily interrupted (29). In addition, propofol decreases cerebral blood flow and lowers intracranial pressure (ICP) (30). If used during several days, however, the dose of propofol should be limited to approximately 80 $\mu\text{g}/\text{kg}$ per min (5 mg/kg per hr) to decrease the risk of propofol infusion syndrome (31).

An opiate infusion is recommended in patients with ALF to prevent or treat discomfort. Agents with shorter half-life, such as fentanyl, are preferred. Morphine and meperidine are not recommended in patients with ALF and renal failure, because active metabolites accumulate, and those of meperidine lower the seizure threshold (29).

Correction of the Bleeding Diathesis. Patients with ALF are, by definition, coagulopathic, and frequently exhibit both quantitative and qualitative platelet dysfunction. Hypofibrinogenemia results from decreased hepatic synthesis as well as increased catabolism (32). However, spontaneous, clinically significant bleeding is uncommon in ALF patients (<10%) (33). Vitamin K deficiency may contribute to the coagulopathy of ALF in a substantial minority of patients (34). Therefore, the administration of vitamin K is recommended empirically in all patients with ALF. Parenteral vitamin K (10 mg intravenously) is recommended, as the absorption of enteral vitamin K may be unreliable (34).

Complete correction of coagulopathy and thrombocytopenia is usually an unobtainable goal in patients with ALF. However, an attempt at improving the bleeding diathesis is recommended in patients with clinically significant bleeding or before placement of invasive devices (35, 36). There are insufficient data to support fixed goals of treatment for standard coagulation times and platelet count in patients with ALF, and these parameters do not necessarily reflect bleeding risk (36, 37). Rough guidelines include an international normalized ratio and platelet count of ~ 1.5 and $\sim 50,000/\text{mm}^3$, respectively (38). Prophylactic fresh frozen plasma to improve coagulopathy in ALF is not recommended, as it does not reduce the risk of significant bleeding nor transfusion requirements, obscures the

trend of prothrombin time as a prognostic marker, and risks volume overload (39). The administration of cryoprecipitate is recommended in patients who have significant hypofibrinogenemia (<100 mg/dL). Antifibrinolytic agents such as aminocaproic acid should be considered in patients with clinical evidence of a hyperfibrinolytic state (diffuse mucosal and puncture wound oozing) and supporting laboratory evidence, such as an increased clot lysis time (40).

Recombinant factor VIIa (rFVIIa) is recommended in circumstances where fresh frozen plasma has failed to correct prothrombin time/international normalized ratio to an acceptable level, or the patient has become volume overloaded, before invasive procedures with a high risk of bleeding (e.g., transjugular liver biopsy or placement of an ICP monitor) (41). Fresh frozen plasma should be administered before rFVIIa to replete other constituents of the clotting cascade, with cryoprecipitate if fibrinogen is <100 mg/dL. rFVIIa (40 $\mu\text{g}/\text{kg}$) should be administered immediately before a planned procedure. The procedure should be performed within 30–60 mins, although the effect of rFVIIa usually persists for >2 hrs (42). The use of rFVIIa may increase the risk of thrombotic complications in patients with ALF (43, 44), especially in higher doses (90 $\mu\text{g}/\text{kg}$) or after repetitive dosing (36). rFVIIa should not be given to patients with a history of myocardial infarction, stroke, or unstable angina within 2 wks, or with active deep venous thrombosis. Patients with ALF due to pregnancy, Budd-Chiari syndrome, or suspected malignant infiltration of the liver also should not receive rFVIIa. In subjects with persistent coagulopathy despite fresh frozen plasma who have contraindications to rFVIIa, plasma exchange is effective and should be considered (45).

The incidence of upper gastrointestinal bleeding in ALF patients has been shown to be decreased by gastric acid suppression with intravenous histamine-2 receptor antagonists (46). Therefore, intravenous histamine-2 blockers, or by inference, proton pump inhibitors (intravenous or oral), are recommended.

Assessment of Prognosis and Liver Transplant Listing Criteria. The ability to predict the likelihood of spontaneous recovery or death without OLT remains of paramount importance in patients with ALF. Many criteria have been proposed to anticipate the probability of death without OLT (Table 2), but there are insuffi-

cient data to recommend a particular scheme, given none have been found to be adequately sensitive and specific. A cursory assessment regarding transplant candidacy should be made on admission to the intensive care unit by the transplant and intensive care teams with specific consideration of poor prognostic factors included in the King's College criteria (Table 2). If no immediate contraindications are identified, an expedited OLT evaluation should be undertaken without delay (47). In addition to the schemes outlined in Table 2, the etiology and rapidity of evolution of ALF also must be considered, because the likelihood of spontaneous recovery without OLT decreases dramatically with the more subacute presentations of fulminant hepatitis B, idiosyncratic drug reactions, and ALF of undetermined etiology (58).

Current requirements for listing a patient with ALF for OLT within the United States must be consistent with Section 3.6.4.1 of the Policies and Bylaws of the United Network for Organ Sharing (available at <http://unos.org>). However, it must be emphasized that these policies are neither objective nor verifiable, nor are they amenable to prospective operational definition. The critical criteria include a) age ≥ 18 yrs; b) a life expectancy without a liver transplant of <7 days; c) onset of hepatic encephalopathy within 8 wks of the first symptoms of liver disease; d) the absence of preexisting liver disease; e) residence in an intensive care unit; and f) at least one of the following: ventilator dependence, requiring renal replacement therapy, or an international normalized ratio >2.0. Patients with acute decompensated Wilson disease also may be listed for OLT because of their universally poor prognosis for spontaneous recovery.

Nutrition. ALF is a catabolic state characterized by negative nitrogen balance and, consequently, immunodeficiency (59). Patients with ALF also exhibit increased resting energy expenditure compared with healthy controls (60). Therefore, nutritional support is recommended in patients with ALF, although essentially no studies exist to guide therapy (60, 61). Enteral nutrition should be administered whenever possible, with higher caloric density feeds preferred to avoid excessive free water and hypo-osmolality, which may exacerbate cerebral edema (see below). Parenteral nutrition (35–40 kcal/kg per day) (61), delivered by a dedicated central venous catheter, should be reserved for patients with specific contraindications to

Table 2. Proposed schemes for assessing prognosis and the need for orthotopic liver transplantation in patients with ALF

Scheme	Etiology of ALF	Criteria for Liver Transplantation ^a	Reference
King's College criteria	APAP	Arterial pH <7.3 OR all of the following: 1) PT >100 secs (INR >6.5) 2) creatinine >3.4 mg/dL 3) grade 3/4 encephalopathy	Dr. O'Grady and colleagues, 1989 (47)
	Non-APAP	PT >100 secs (INR >6.5) OR any 3 of the following: 1) NANB/drug/halothane etiology 2) jaundice to encephalopathy > 7 days 3) age <10 or >40 yrs 4) PT >50 secs (INR >3.5) 5) bilirubin >17.4 mg/dL	
Factor V	Viral	Age <30 yrs: factor V <20% OR Any age: factor V <30% and grade 3/4 encephalopathy	Dr. Bernuau and colleagues (48, 49)
Factor VIII/V ratio	APAP	Factor VIII/V ratio >30	Dr. Pereira and colleagues (50)
Liver biopsy	Mixed	Hepatocyte necrosis >70%	Dr. Donaldson and colleagues (51)
Severity index	HBV, NANB	See reference	Dr. Takahashi and colleagues (52)
Arterial phosphate	APAP	>1.2 mmol/L	Dr. Schmidt and colleagues (53)
Arterial lactate	APAP	>3.5 mmol/L	Dr. Bernal and colleagues (54)
Arterial ammonia	Mixed	>150–200 μmol/L	Dr. Clemmesen and colleagues (55)
APACHE II score	APAP	Score >15	Dr. Mitchell and colleagues (56)
MELD/ΔMELD score	APAP	MELD >33 ΔMELD >−0.4	Dr. Schmidt and colleagues (57)

ALF, acute liver failure; APAP, acetaminophen; PT, prothrombin time; INR, international normalized ratio; NANB, non-A, non-B viral hepatitis; Mixed, mixed etiologies; HBV, hepatitis B virus; APACHE, Acute Physiology and Chronic Health Evaluation; MELD, Model for End-Stage Liver Disease.

^aTimes of data collection vary between studies. See individual references.

enteral nutrition. Monitoring for blood glucose should be performed at frequent regular intervals by finger stick (e.g., every 1–2 hrs). Intravenous glucose infusion (1.5–2.0 g/kg per day) is recommended in patients who develop hypoglycemia. Although single center clinical trials have suggested that the maintenance of tight glycemic control reduces mortality in critically ill patients (62, 63), and hyperglycemia may exacerbate intracranial hypertension in patients with ALF (64), ALF patients are at high risk for hypoglycemia. Thus, until further information is available, it is recommended that insulin infusions be used to maintain blood glucose levels <150 mg/dL, while also strictly avoiding hypoglycemia. Approximately 40 g protein per day (0.5–1.0 g/kg per day) also should be administered (65). There are insufficient data to recommend the use of branched-chain amino acids, which are also limited by cost (66). Lipid emulsions appear to be safe in ALF patients, and are recommended as a concentrated source of calories in volume-overloaded patients (61).

Seizure Prophylaxis and Surveillance. Nonconvulsive seizure activity has been documented in a high proportion of patients with ALF and advanced stages of hepatic encephalopathy (67). However, there are insufficient data to recommend prophylactic anticonvulsants in all patients with ALF, because two studies using prophylactic phenytoin have reached conflicting conclusions (67, 68). It should

be noted that propofol or benzodiazepine infusions used for sedation also provide potent antiseizure prophylaxis.

The performance of electroencephalogram, not necessarily continuously, is recommended for the following indications (68): a) grade III or intravenous hepatic encephalopathy; b) sudden unexplained deterioration in neurologic examination; c) myoclonus; or d) to titrate therapy when barbiturate coma is used to manage cerebral edema.

Treatment of Circulatory Dysfunction. In hypotensive patients with ALF, volume status should be assessed and hypovolemia corrected before the administration of vasopressors. Vasopressors are recommended for severe systemic hypotension (systolic blood pressure <90 mm Hg; mean arterial pressure <65 mm Hg) or to maintain a cerebral perfusion pressure (CPP)(equivalent to mean arterial pressure – ICP) of 50–80 mm Hg. Norepinephrine or dopamine are recommended, with norepinephrine preferred, because the former may provide a more consistent and predictable increase in cerebral perfusion than the latter in patients with traumatic brain injury (69). Low-dose dopamine is not recommended, as it has not been shown to be effective in decreasing the risk of renal failure in patients with systemic inflammatory response syndrome and early renal dysfunction (70). Epinephrine has been shown to decrease mesenteric blood flow in severe septic shock, and therefore may compro-

mise hepatic blood flow in patients with ALF (71, 72). Vasopressin and analogs are not recommended, because they directly cause cerebral vasodilation and may exacerbate intracranial hypertension (73).

Relative adrenal insufficiency occurs frequently in patients with ALF, and may contribute to cardiovascular collapse (74). Moderate doses (200–300 mg/day) of hydrocortisone have been shown to improve the vasopressor response to norepinephrine in hypotensive patients with sepsis (75) and ALF (76). A trial of hydrocortisone should be considered in ALF patients with persistent hypotension despite a volume challenge and norepinephrine. Because of conflicting results in clinical trials, there are insufficient data to recommend the use of agents which purportedly improve peripheral tissue oxygenation, such as prostacyclin (77) and *N*-acetylcysteine (78, 79).

MANAGEMENT OF CEREBRAL EDEMA AND INTRACRANIAL HYPERTENSION

Intracranial hypertension due to cerebral edema remains one of the primary causes of morbidity and mortality in patients with ALF (80), with highest incidence in patients with more acute presentations (i.e., a jaundice-to-encephalopathy interval of <4 wks) (58). A head computed tomography is recommended in patients with ALF who progress to stage III/IV hepatic encephalopathy or experience an

acute change in mental status, or before ICP monitor placement. Although a head computed tomography will frequently demonstrate cerebral edema in ALF patients with advanced-stage hepatic encephalopathy (81), it is insensitive to intracranial hypertension (82, 83); therefore, its principal value is to rule out other uncommon intracranial pathology, most importantly bleeding. The physician must consider the potential risk of moving a patient from the intensive care unit to the computed tomography scanner.

The indications for placement of an ICP monitor remain one of the most contentious issues in managing patients with ALF, because there are no randomized, controlled studies to guide the physician. Indeed, ICP monitoring in nonrandomized subjects has not been shown to improve survival (84, 85). Therefore, there are insufficient data to recommend ICP monitor placement in all patients with ALF. However, most members of the ALFSG place ICP monitors in patients with advanced (stage III/IV) hepatic encephalopathy with the belief that monitoring improves the management of cerebral edema and provides important prognostic information regarding neurologic recovery after OLT (84, 85). Therefore, ICP monitor placement should be considered in all patients listed for OLT with stage III/IV hepatic encephalopathy. Some centers also insert ICP monitors in non-OLT candidates with advanced stage hepatic encephalopathy in whom intensive medical management offers a reasonable likelihood of spontaneous survival (e.g., in patients with acetaminophen-induced ALF).

Bleeding complications attributed to the placement of ICP monitors occur in 10% to 20% of patients with ALF, but are often mild and of questionable clinical significance (84–86). Therefore, treatment of the bleeding diathesis before insertion is recommended as outlined above. There are insufficient data to recommend a standard intracranial location for ICP monitor placement. While it has been observed that placement of ICP monitors in the epidural space may decrease the incidence of bleeding complications (84, 86), such monitors are less accurate than those that traverse the dura and they tend to overestimate ICP (87). Due to the risk of bleeding, intraventricular placement should be avoided. ICP monitor placement is not recommended in patients with mild hepatic encephalopathy (stages I/II), or with clinical

evidence of diencephalic herniation and/or intractable arterial hypotension, in whom death is imminent.

Management of Intracranial Hypertension: General Recommendations. A quiet environment with limited stimulation is recommended for ALF patients with evidence of cerebral edema. Chest physiotherapy and endotracheal suctioning also may need to be minimized, and prophylactic intravenous lidocaine before endotracheal suctioning may be considered (88). To decrease ICP, the head should be maintained in a neutral position (89), and the head of the bed should be elevated to 30 degrees (90, 91), which will also reduce the risk of ventilator-associated aspiration pneumonia (92). During elevation of the head of the bed, mean arterial pressure should be maintained to avoid decreasing the cerebral perfusion pressure (93). Trendelenburg position, head flexion, head rotation, and sudden change of position to supine should be avoided except when necessary for placement of a central venous catheter (89).

Hyperventilation-induced hypocapnia induces cerebral vasoconstriction, decreases ICP (94, 95), and may improve cerebrovascular autoregulation (96). Spontaneous hyperventilation, therefore, which is usual in patients with ALF, should not be treated. However, prophylactic hyperventilation is not recommended in patients with ALF, because vasoconstriction can reduce cerebral oxygen utilization (94) and had no effect on the development of cerebral edema in one study (97). Consequently, maintenance of a P_{CO_2} between 30 and 40 mm Hg is a reasonable goal. Acute hyperventilation, however, is recommended as emergency rescue therapy of patients with evidence of diencephalic herniation.

Generally, maintenance of euthermia (36.5–37.5°C) is recommended in patients with ALF, because fever exacerbates intracranial hypertension (25) and is independently associated with worse outcome in patients admitted to neurologic intensive care units (98). Fever should be treated aggressively with cooling blankets, fans, or other noninvasive devices, but nonsteroidal anti-inflammatory drugs and acetaminophen are not recommended because of possible nephro- and gastric mucosal toxicity, and possible potentiation of liver injury, respectively. Shivering, which may also increase ICP, should be treated with increased sedation, or with small doses of

meperidine (12.5–25 mg). Mild spontaneous hypothermia (35–36.5°C), such as that observed during continuous renal replacement therapy, should not be treated. At this time, there are insufficient data to support the routine use of prophylactic hypothermia in patients with ALF. However, the induction of hypothermia may be considered in the treatment of intracranial hypertension refractory to mannitol (see below).

Cerebral edema in ALF results primarily from astrocyte swelling (cytotoxic cerebral edema) rather than a leaky blood brain barrier (vasogenic cerebral edema) (99). While vasogenic cerebral edema may respond to corticosteroids, cerebral edema in ALF has not been shown to improve after their administration (100); therefore, corticosteroids are not recommended.

Management of Intracranial Hypertension: Specific Recommendations. The absolute values and duration of abnormal ICP and CPP for optimal neurologic recovery after ALF have not been well defined. Therefore, there are insufficient data to recommend strict pressure goals. Suggested ICP based upon experience of individual liver transplant centers in patients with ALF (83, 101), and of other centers in patients with traumatic brain injury (102), include an ICP of <25 mm Hg and CPP between 50 and 80 mm Hg. There are also insufficient data to recommend criteria of ICP and CPP to contraindicate OLT, because rare cases of complete neurologic recovery after severe, prolonged, intracranial hypertension have been reported (103). It has been observed that severe (>40 mm Hg), sustained, intracranial hypertension refractory to medical therapy and/or a CPP <40 mm Hg for >2 hrs are associated with brainstem herniation or poor neurologic recovery after OLT (83). However, if a patient's pupils remain reactive and a liver graft becomes available, some transplant surgeons would proceed with OLT (103).

The administration of mannitol is recommended as first-line therapy for intracranial hypertension. Mannitol should be administered when ICP \geq 25 mm Hg for >10 mins, after the validity of the ICP calibration is confirmed. There are insufficient data to recommend a standard dose of mannitol to be administered. A range of doses (0.25–1.0 g/kg intravenous boluses) has been used both in patients with brain injury (104) and ALF (94, 105). Because lower doses reduce the risk of

severe osmotic disequilibrium and dehydration, and may be as effective as higher doses (104), 0.25–0.5 g/kg boluses are recommended. Serum osmolality should be assessed every 6 hrs, and mannitol boluses may be repeated if ICP remains >25 mm Hg and serum osmolality <320 mOsm/L. It should be noted that serum osmolality correlates poorly with mannitol concentrations, and a normal osmolar gap may be a more accurate measure of adequate mannitol clearance before the administration of subsequent doses (106).

There are insufficient data to recommend a standard therapy of intracranial hypertension refractory to mannitol. However, the following may be considered in the following order based upon ease and safety of administration, and efficacy based upon the available literature.

Hypertonic saline boluses have been used increasingly in neurocritical care patients, with efficacy similar or superior to mannitol (107–111). Many preparations and dosing strategies of hypertonic saline have been employed to treat cerebral edema, including 23.4% saline (30 mL) and 7.5% saline (2.0 mL/kg) boluses repeated every 2 hrs to 3 hrs (111). Serum sodium should be monitored at frequent intervals. Hypertonic saline also has been administered prophylactically to ALF patients with high grade encephalopathy as a constant infusion (30%, 5–20 mL/hr) to achieve a serum sodium of 145 mmol/L to 155 mmol/L. In one small, randomized trial, the incidence and severity of intracranial hypertension was reduced in those patients with induced hyponatremia (112). Although hyponatremia of short duration is not a contraindication to administering hypertonic saline in patients with ALF, the rate of correction should be inversely proportional to the duration of hyponatremia to minimize the risk of osmotic demyelination.

Induced moderate hypothermia (32–33°C) may decrease ICP in ALF patients with intracranial hypertension refractory to mannitol (113), and stabilize ICP during OLT (114). Increasingly, units within the ALFSG have used hypothermia to bridge patients with osmotherapy-refractory intracranial hypertension to OLT, although the practice is not universally endorsed. Further studies also must document the safety of the practice, which may increase the risk of cardiovascular instability and/or infection.

Barbiturate coma, induced by pentobarbital (3–5 mg/kg intravenous loading bolus followed by 1–3 mg/kg per hr in-

travenous infusion) or thiopental (5–10 mg/kg loading bolus followed by 3–5 mg/kg per hr), also has been advocated in patients with ALF refractory to mannitol (83, 115). Potential severe adverse effects—including hypotension, hypothermia, immunosuppression, hypokalemia, and prolonged coma—mandate physician experience with the induction of barbiturate coma, and vasopressors to maintain cerebral perfusion pressure >50 mm Hg usually are required.

Indomethacin (25 mg infused intravenously for 1 min) also has been shown to acutely decrease ICP and increase CPP by causing cerebral vasoconstriction (116, 117). Indomethacin therefore may be considered as salvage therapy in patients with intracranial hypertension refractory to the above measures.

OTHER SPECIAL PROCEDURES

Mechanical Ventilation. Recommended indications for endotracheal intubation include respiratory failure (hypoxemia, hypercapnia), airway protection in the setting of advanced encephalopathy (stage III/IV), agitation, and imminent ICP monitor placement. Laryngoscopy and endotracheal intubation may be associated with transient elevation in ICP and appropriate countermeasures (induction of anesthesia followed by constant sedation) are recommended.

There are insufficient data to recommend a standard mode of delivering mechanical ventilation to patients with ALF. Patients with ALF often develop acute respiratory distress syndrome with disease progression to cerebral edema (118), often in the setting of infection as part of systemic inflammatory response syndrome (24). Generally, tidal volume and plateau pressure should be limited (6 mL/kg predicted body weight and <30 cm H₂O, respectively) in intensive care unit patients with established acute lung injury, and low tidal volumes also may decrease the risk of progression to acute respiratory distress syndrome (119, 120). It must be appreciated that decrements in tidal volume will decrease minute ventilation and increase Pco₂, and thereby increase ICP. Therefore, in patients with low tidal volumes, the respiratory rate should be increased to maintain a stable Pco₂.

High levels of positive end-expiratory pressure also may increase ICP in patients with ALF, and decrease hepatic blood flow (121). However, in neuro-

critical care patients, the effects of positive end-expiratory pressure on ICP are inconsistent and not always clinically important (122). In general, the lowest level of positive end-expiratory pressure that achieves adequate oxygenation should be applied in patients with ALF.

Renal Replacement Therapy (RRT); Management of Fluids and Electrolytes. The evaluation of acute renal failure in patients with ALF should include analysis of urine sodium, which is low (<10 mEq/L) in prerenal azotemia and functional renal failure (hepatorenal syndrome) and high in acute tubular necrosis. Microscopic examination of the urine should be performed to detect casts and renal tubular cells, which suggest acute tubular necrosis. Assessment of intravascular volume by measurement of central venous pressure, or pulmonary capillary wedge pressure via pulmonary artery catheter, may be considered, but these measures poorly reflect intravascular volume (123). An intravenous fluid challenge (crystalloid and colloid; 1–1.5 L) is recommended to exclude prerenal azotemia, but large volumes of glucose-containing solutions should be avoided in consideration of the risk of hyperglycemia.

There are insufficient data to recommend specific criteria to start or discontinue renal replacement therapy (RRT) in patients with ALF. However, the decision to start RRT should be based upon the level of renal dysfunction, fluid balance, and metabolic derangements, and a need to create space for intravenous colloid (e.g., fresh frozen plasma) or parenteral nutrition. Goals of RRT should be clearly delineated before initiation of RRT. Conversely, a plan for discontinuing RRT also should be agreed upon before its institution, particularly in the event that a patient is no longer considered for OLT or fails to spontaneously improve (124).

Patients with ALF frequently tolerate intermittent hemodialysis poorly because of hemodynamic instability and fluid shifts. Furthermore, intermittent hemodialysis may increase ICP (125). Therefore, most members of the ALFSG prefer continuous RRT (126), even in hemodynamically stable patients (127). Mannitol removal may be accomplished by high volume continuous venovenous hemofiltration, but has not been well studied; conventional hemodialysis or continuous venovenous hemodiafiltration may be required for this purpose (128). A dedicated double-lumen catheter inserted in the internal jugular vein is recommended, un-

less the patient has significant intracranial hypertension, in which case the femoral route is preferred. If the catheter remains in place for >7 days, a tunneled catheter should be considered. Catheters should be locked with saline or citrate. During continuous venovenous hemofiltration, heparin anticoagulation should be avoided because of the risk of bleeding, and citrate is recommended, although ionized serum calcium must be monitored carefully. Bicarbonate buffer solutions are recommended, because citrate and lactate both require biotransformation to bicarbonate in the liver.

Electrolyte abnormalities of all types frequently accompany ALF, especially when complicated by renal failure, and may be particularly deleterious. Monitoring of serum electrolyte concentrations (once or twice daily) and prompt correction of abnormalities is recommended. Hyponatremia should be strictly avoided, because it may exacerbate cerebral edema. As noted above, a relative restriction of free water is recommended; for example, by administering higher caloric density enteral feeds and/or more concentrated glucose infusions in ALF patients with hypoglycemia. Although there are insufficient data to advise a rate of correction of serum sodium, the risk of osmotic demyelination may be lower than in other patient populations because of the short duration of hyponatremia. Therefore, hypertonic saline boluses or continuous RRT may be employed for this purpose (126), with adjustment of the rate of correction for the length of time of hyponatremia. Other electrolyte concentrations (phosphate, magnesium, bicarbonate) should be kept within the normal range.

Maintenance of euvolemia in ALF is recommended to avoid hemodynamic instability and underperfusion of critical vascular beds. Unfortunately, central venous pressure and pulmonary capillary wedge pressure reflect intravascular volume unreliably, and hypotensive ALF patients should first receive a volume challenge, as above. In volume-unresponsive subjects, echocardiography or other non-invasive measures of intrathoracic blood volume should be considered.

MANAGEMENT OF ALF DURING AND AFTER OLT

Many complications of ALF persist or become more acute during OLT. Unfortunately, there are insufficient data from

clinical trials to recommend any specific management decision pertaining to OLT in ALF patients. However, based upon practices in the published literature and the experiences of centers in the ALFSG, the following guidelines have been endorsed.

Intraoperative and Postoperative Monitoring. ICP frequently increases during dissection of the native liver and during reperfusion of the graft (114), especially if the patient has experienced intracranial hypertension before OLT (129). Furthermore, intracranial hypertension may persist during the first 10–12 hrs after OLT for ALF (130). Therefore, if an ICP monitor has been placed before OLT, ICP should be continuously monitored during and early after OLT. OLT should not be delayed, however, for placement of an ICP monitor after an organ has become available, as long as the patient's pupils remain active and the patient is not posturing (131). Monitoring in the operating suite also should include continuous arterial pressure. As in the case of pre-liver transplant patients, pressure goals include ICP <25 mm Hg, mean arterial pressure >90 mm Hg, and CPP 50 mm Hg to 80 mm Hg, and norepinephrine is preferred for pressor support (114). Osmotherapy with mannitol should be administered for ICP \geq 25 mm Hg for >10 mins, and serum sodium should be maintained between 140–150 mmol/L.

Graft Selection Considerations. Survival after OLT for ALF decreases markedly after patients have progressed to stage IV hepatic encephalopathy (131). Therefore, in patients deemed to have poor prognosis by the schemes outlined in Table 2, OLT must be performed as soon as an organ becomes available and not delayed. In general, ABO-identical grafts are preferred, but ABO-compatible grafts have nearly comparable 1-yr survival after OLT for ALF and should be used without hesitation (132). The gravity of the clinical situation must dictate whether to use an ABO-incompatible graft, because 1-yr graft survival is decidedly lower (132). Evaluation of a possible living donor may be entertained by transplant centers with extensive experience with living donor liver transplantation in cirrhotic patients. Such an expedited evaluation has been shown to be feasible in the setting of ALF, with outcomes as good as OLT with a deceased donor graft (133).

Other Surgical Considerations. Transplant surgeons generally tailor other de-

isions regarding the surgical management of ALF patients to the particular clinical situation. Venovenous bypass has been advocated by some authorities (132), but not others (114), to minimize swings in cerebral perfusion during clamping of the inferior vena cava and portal vein, as well as during reperfusion. Similarly, hepatectomy of the native liver with temporary portocaval anastomosis may be considered in ALF patients with toxic liver syndrome (134–136). (5–57)

ACKNOWLEDGMENTS

While the opinions expressed herein do not entirely reflect their practices, the authors wish to acknowledge the thoughtful comments of Drs. Julia Wendon (King's College Hospital, London, UK) and Fin Larsen (University Hospital of Copenhagen, Denmark).

REFERENCES

1. Lee WM: Acute liver failure in the United States. *Semin Liver Dis* 2003; 23:217–226
2. Polson J, Lee WM: AASLD position paper: The management of acute liver failure. *Hepatology* 2005; 41:1179–1197
3. Makin A, Williams R: Acetaminophen-induced acute liver failure. *In: Acute Liver Failure*. First Edition. Lee WM, Williams R (Eds). Cambridge, UK, Cambridge University Press, 1997, pp 32–42
4. Mabie WC: Acute fatty liver of pregnancy. *Crit Care Clin* 1991; 7:799–808
5. Smilkstein MJ, Knapp GL, Kulig KW, et al: Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). *N Engl J Med* 1988; 319: 1557–1562
6. Buckley NA, Whyte IM, O'Connell DL, et al: Oral or intravenous N-acetylcysteine: Which is the treatment of choice for acetaminophen (paracetamol) poisoning? *J Toxicol Clin Toxicol* 1999; 37:759–767
7. Smilkstein MJ, Bronstein AC, Linden C, et al: Acetaminophen overdose: A 48-hour intravenous N-acetylcysteine treatment protocol. *Ann Emerg Med* 1991; 20:1058–1063
8. Floersheim GL, Eberhard M, Tschumi P, et al: Effects of penicillin and silymarin on liver enzymes and blood clotting factors in dogs given a boiled preparation of *Amanita phalloides*. *Toxicol Appl Pharmacol* 1978; 46:455–462
9. Broussard CN, Aggarwal A, Lacey SR, et al: Mushroom poisoning—from diarrhea to liver transplantation. *Am J Gastroenterol* 2001; 96:3195–3198
10. Peters DJ, Greene WH, Ruggiero F, et al: *Herpes simplex*-induced fulminant hepatitis in adults: A call for empiric therapy. *Dig Dis Sci* 2000; 45:2399–2404

11. Kessler WR, Cummings OW, Eckert G, et al: Fulminant hepatic failure as the initial presentation of acute autoimmune hepatitis. *Clin Gastroenterol Hepatol* 2004; 2: 625–631
12. Tillmann HL, Hadem J, Leifeld L, et al: Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. *J Viral Hepat* 2006; 13:256–263
13. Castro MA, Fassett MJ, Reynolds TB, et al: Reversible peripartum liver failure: A new perspective on the diagnosis, treatment, and cause of acute fatty liver of pregnancy, based on 28 consecutive cases. *Am J Obstet Gynecol* 1999; 181:389–395
14. Blei AT: Pathophysiology of brain edema in fulminant hepatic failure, revisited. *Metab Brain Dis* 2001; 16:85–94
15. Alba L, Hay J, Angulo P, et al: Lactulose therapy in acute liver failure. *J Hepatol* 2002; 36:33A
16. Wright RA: Lactulose-induced megacolon. *Gastrointest Endosc* 1988; 34:489–490
17. Kaupke C, Sprague T, Gitnick GL: Hypernatremia after the administration of lactulose. *Ann Intern Med* 1977; 86:745–746
18. Greenberg LH, Momary H: Audiotoxicity and nephrotoxicity due to orally administered neomycin. *JAMA* 1965; 194:827–828
19. Rolando N, Philpott-Howard J, Williams R: Bacterial and fungal infection in acute liver failure. *Semin Liver Dis* 1996; 16:389–402
20. Rolando N, Harvey F, Brahm J, et al: Prospective study of bacterial infection in acute liver failure: An analysis of fifty patients. *Hepatology* 1990; 11:49–53
21. Rolando N, Harvey F, Brahm J, et al: Fungal infection: A common, unrecognised complication of acute liver failure. *J Hepatol* 1991; 12:1–9
22. Vaquero J, Polson J, Chung C, et al: Infection and the progression of hepatic encephalopathy in acute liver failure. *Gastroenterology* 2003; 125:755–764
23. Rolando N, Gimson A, Wade J, et al: Prospective controlled trial of selective parenteral and enteral antimicrobial regimen in fulminant liver failure. *Hepatology* 1993; 17:196–201
24. Rolando N, Wade J, Davalos M, et al: The systemic inflammatory response syndrome in acute liver failure. *Hepatology* 2000; 32(4 Pt 1):734–739
25. Munoz SJ, Moritz MJ, Bell R, et al: Factors associated with severe intracranial hypertension in candidates for emergency liver transplantation. *Transplantation* 1993; 55: 1071–1074
26. Citerio G, Cormio M: Sedation in neurointensive care: Advances in understanding and practice. *Curr Opin Crit Care* 2003; 9:120–126
27. Basile AS, Hughes RD, Harrison PM, et al: Elevated brain concentrations of 1,4-benzodiazepines in fulminant hepatic failure. *N Engl J Med* 1991; 325:473–478
28. Marik PE: Propofol: Therapeutic indications and side-effects. *Curr Pharm Des* 2004; 10: 3639–3649
29. Jacobi J, Fraser GL, Coursin DB, et al: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002; 30: 119–141
30. Wijdicks EF, Nyberg SL: Propofol to control intracranial pressure in fulminant hepatic failure. *Transplant Proc* 2002; 34:1220–1222
31. Cremer OL, Moons KG, Bouman EA, et al: Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet* 2001; 357:117–118
32. Clark RD, Gazzard BG, Lewis ML, et al: Fibrinogen metabolism in acute hepatitis and active chronic hepatitis. *Br J Haematol* 1975; 30:95–102
33. Gazzard BG, Clark R, Borirakchanyavat V, et al: A controlled trial of heparin therapy in the coagulation defect of paracetamol-induced hepatic necrosis. *Gut* 1974; 15: 89–93
34. Pereira SP, Rowbotham D, Fitt S, et al: Pharmacokinetics and efficacy of oral versus intravenous mixed-micellar phyloquinone (vitamin K1) in severe acute liver disease. *J Hepatol* 2005; 42:365–370
35. Pereira SP, Langley PG, Williams R: The management of abnormalities of hemostasis in acute liver failure. *Semin Liver Dis* 1996; 16:403–414
36. Caldwell SH, Chang C, Macik BG: Recombinant activated factor VII (rFVIIa) as a hemostatic agent in liver disease: A break from convention in need of controlled trials. *Hepatology* 2004; 39:592–598
37. Boks AL, Brommer EJ, Schalm SW, et al: Hemostasis and fibrinolysis in severe liver failure and their relation to hemorrhage. *Hepatology* 1986; 6:79–86
38. Drews RE, Weinberger SE: Thrombocytopenic disorders in critically ill patients. *Am J Respir Crit Care Med* 2000; 162(2 Pt 1): 347–351
39. Gazzard BG, Henderson JM, Williams R: Early changes in coagulation following a paracetamol overdose and a controlled trial of fresh frozen plasma therapy. *Gut* 1975; 16:617–620
40. Lisman T, Leebeek FW, Meijer K, et al: Recombinant factor VIIa improves clot formation but not fibrolytic potential in patients with cirrhosis and during liver transplantation. *Hepatology* 2002; 35:616–621
41. Shami VM, Caldwell SH, Hespeneheide EE, et al: Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. *Liver Transpl* 2003; 9:138–143
42. Jeffers L, Chalasani N, Balart L, et al: Safety and efficacy of recombinant factor VIIa in patients with liver disease undergoing laparoscopic liver biopsy. *Gastroenterology* 2002; 123:118–126
43. Porte RJ, Caldwell SH: The role of recombinant factor VIIa in liver transplantation. *Liver Transpl* 2005; 11:872–874
44. Pavese P, Bonadona A, Beaubien J, et al: FVIIa corrects the coagulopathy of fulminant hepatic failure but may be associated with thrombosis: A report of four cases. *Can J Anaesth* 2005; 52:26–29
45. Munoz SJ, Ballas SK, Moritz MJ, et al: Perioperative management of fulminant and subfulminant hepatic failure with therapeutic plasmapheresis. *Transplant Proc* 1989; 21:3535–3536
46. MacDougall BR, Williams R: H2-receptor antagonist in the prevention of acute upper gastrointestinal hemorrhage in fulminant hepatic failure: A controlled trial. *Gastroenterology* 1978; 74(2 Pt 2):464–465
47. O'Grady JG, Alexander GJ, Hayllar KM, et al: Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; 97: 439–445
48. Bernuau J, Goudeau A, Poynard T, et al: Multivariate analysis of prognostic factors in fulminant hepatitis B. *Hepatology* 1986; 6:648–651
49. Bernuau J, Samuel D, Durand F, et al: Criteria for emergency liver transplantation in patients with acute viral hepatitis and factor V below 50% of normal: A prospective study. *Abstr. Hepatology* 1991; 14:49A
50. Pereira LM, Langley PG, Hayllar KM, et al: Coagulation factor V and VIII/V ratio as predictors of outcome in paracetamol-induced fulminant hepatic failure: Relation to other prognostic indicators. *Gut* 1992; 33:98–102
51. Donaldson BW, Gopinath R, Wanless IR, et al: The role of transjugular liver biopsy in fulminant liver failure: Relation to other prognostic indicators. *Hepatology* 1993; 18: 1370–1376
52. Takahashi Y, Kumada H, Shimizu M, et al: A multicenter study on the prognosis of fulminant viral hepatitis: Early prediction for liver transplantation. *Hepatology* 1994; 19: 1065–1071
53. Schmidt LE, Dalhoff K: Serum phosphate is an early predictor of outcome in severe acetaminophen-induced hepatotoxicity. *Hepatology* 2002; 36:659–665
54. Bernal W, Donaldson N, Wyncoll D, et al: Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: A cohort study. *Lancet* 2002; 359:558–563
55. Clemmesen JO, Larsen FS, Kondrup J, et al: Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. *Hepatology* 1999; 29: 648–653
56. Mitchell I, Bihari D, Chang R, et al: Earlier identification of patients at risk from acetaminophen-induced acute liver failure. *Crit Care Med* 1998; 26:279–284
57. Schmidt LE, Larsen FS: MELD score as a predictor of liver failure and death in patients with acetaminophen-induced liver injury. *Hepatology* 2007; 45:789–796
58. O'Grady JG, Schalm SW, Williams R: Acute liver failure: Redefining the syndromes. *Lancet* 1993; 342:273–275
59. O'Keefe SJ, El Zayadi AR, Carraher TE, et al:

- Malnutrition and immuno-incompetence in patients with liver disease. *Lancet* 1980; 2:615–617
60. Walsh TS, Wigmore SJ, Hopton P, et al: Energy expenditure in acetaminophen-induced fulminant hepatic failure. *Crit Care Med* 2000; 28:649–654
 61. Munoz SJ: Nutritional therapies in liver disease. *Semin Liver Dis* 1991; 11:278–291
 62. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449–461
 63. Van den BG, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al: Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345:1359–1367
 64. Kodakat S, Gopal P, Wendon J: Hyperglycaemia is associated with intracranial hypertension in patients with acute liver failure. *Abstr. Liver Transpl* 2001; 7:C-21
 65. Chase RA, Davies M, Trewby PN, et al: Plasma amino acid profiles in patients with fulminant hepatic failure treated by repeated polyacrylonitrile membrane hemodialysis. *Gastroenterology* 1978; 75:1033–1040
 66. Schutz T, Bechstein WO, Neuhaus P, et al: Clinical practice of nutrition in acute liver failure—a European survey. *Clin Nutr* 2004; 23:975–982
 67. Ellis AJ, Wendon JA, Williams R: Subclinical seizure activity and prophylactic phenytoin infusion in acute liver failure: A controlled clinical trial. *Hepatology* 2000; 32: 536–541
 68. Bhatia V, Batra Y, Acharya SK: Prophylactic phenytoin does not improve cerebral edema or survival in acute liver failure—a controlled clinical trial. *J Hepatol* 2004; 41: 89–96
 69. Steiner LA, Johnston AJ, Czosnyka M, et al: Direct comparison of cerebrovascular effects of norepinephrine and dopamine in head-injured patients. *Crit Care Med* 2004; 32:1049–1054
 70. Bellomo R, Chapman M, Finfer S, et al: Low-dose dopamine in patients with early renal dysfunction: A placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet* 2000; 356: 2139–2143
 71. De Backer D, Creteur J, Silva E, et al: Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: Which is best? *Crit Care Med* 2003; 31:1659–1667
 72. Holmes CL: Vasoactive drugs in the intensive care unit. *Curr Opin Crit Care* 2005; 11:413–417
 73. Shawcross DL, Davies NA, Mookerjee RP, et al: Worsening of cerebral hyperemia by the administration of terlipressin in acute liver failure with severe encephalopathy. *Hepatology* 2004; 39:471–475
 74. Harry R, Auzinger G, Wendon J: The clinical importance of adrenal insufficiency in acute hepatic dysfunction. *Hepatology* 2002; 36:395–402
 75. Annane D, Sebille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862–871
 76. Harry R, Auzinger G, Wendon J: The effects of supraphysiological doses of corticosteroids in hypotensive liver failure. *Liver Int* 2003; 23:71–77
 77. Wendon JA, Harrison PM, Keays R, et al: Effects of vasopressor agents and epoprostenol on systemic hemodynamics and oxygen transport in fulminant hepatic failure. *Hepatology* 1992; 15:1067–1071
 78. Harrison PM, Wendon JA, Gimson AE, et al: Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. *N Engl J Med* 1991; 324: 1852–1857
 79. Walsh TS, Hopton P, Philips BJ, et al: The effect of N-acetylcysteine on oxygen transport and uptake in patients with fulminant hepatic failure. *Hepatology* 1998; 27: 1332–1340
 80. Ware AJ, D'Agostino AN, Combes B: Cerebral edema: A major complication of massive hepatic necrosis. *Gastroenterology* 1971; 61:877–884
 81. Wijdicks EF, Plevak DJ, Rakela J, et al: Clinical and radiologic features of cerebral edema in fulminant hepatic failure. *Mayo Clin Proc* 1995; 70:119–124
 82. Munoz SJ, Robinson M, Northrup B, et al: Elevated intracranial pressure and computed tomography of the brain in fulminant hepatocellular failure. *Hepatology* 1991; 13: 209–212
 83. Lidofsky SD, Bass NM, Prager MC, et al: Intracranial pressure monitoring and liver transplantation for fulminant hepatic failure. *Hepatology* 1992; 16:1–7
 84. Keays RT, Alexander GJ, Williams R: The safety and value of extradural intracranial pressure monitors in fulminant hepatic failure. *J Hepatol* 1993; 18:205–209
 85. Vaquero J, Fontana RJ, Larson AM, et al: Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. *Liver Transpl* 2005; 11:1581–1589
 86. Blei AT, Olafsson S, Webster S, et al: Complications of intracranial pressure monitoring in fulminant hepatic failure. *Lancet* 1993; 341:157–158
 87. Poca MA, Sahuquillo J, Topczewski T, et al: Is intracranial pressure monitoring in the epidural space reliable? Fact and fiction. *J Neurosurg* 2007; 106:548–556
 88. Yano M, Nishiyama H, Yokota H, et al: Effect of lidocaine on ICP response to endotracheal suctioning. *Anesthesiology* 1986; 64:651–653
 89. Mavrocordatos P, Bissonnette B, Ravussin P: Effects of neck position and head elevation on intracranial pressure in anesthetized neurosurgical patients: Preliminary results. *J Neurosurg Anesthesiol* 2000; 12:10–14
 90. Herrine S, Northrup B, Bell R, et al: The effect of head elevation on cerebral perfusion pressure in fulminant hepatic failure. *Hepatology* 1995; 22:289A
 91. Ng I, Lim J, Wong HB: Effects of head posture on cerebral hemodynamics: Its influences on intracranial pressure, cerebral perfusion pressure, and cerebral oxygenation. *Neurosurgery* 2004; 54:593–597
 92. Dodek P, Keenan S, Cook D, et al: Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med* 2004; 141:305–313
 93. Rosner MJ, Coley IB: Cerebral perfusion pressure, intracranial pressure, and head elevation. *J Neurosurg* 1986; 65:636–641
 94. Wendon JA, Harrison PM, Keays R, et al: Cerebral blood flow and metabolism in fulminant liver failure. *Hepatology* 1994; 19: 1407–1413
 95. Strauss GI, Moller K, Holm S, et al: Transcranial doppler sonography and internal jugular bulb saturation during hyperventilation in patients with fulminant hepatic failure. *Liver Transpl* 2001; 7:352–358
 96. Strauss G, Hansen BA, Knudsen GM, et al: Hyperventilation restores cerebral blood flow autoregulation in patients with acute liver failure. *J Hepatol* 1998; 28:199–203
 97. Ede RJ, Gimson AE, Bihari D, et al: Controlled hyperventilation in the prevention of cerebral oedema in fulminant hepatic failure. *J Hepatol* 1986; 2:43–51
 98. Diringier MN, Reaven NL, Funk SE, et al: Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. *Crit Care Med* 2004; 32:1489–1495
 99. Ranjan P, Mishra AM, Kale R, et al: Cytotoxic edema is responsible for raised intracranial pressure in fulminant hepatic failure: *In vivo* demonstration using diffusion-weighted MRI in human subjects. *Metab Brain Dis* 2005; 20:181–192
 100. Report from the European Association for the Study of the Liver (EASL): Randomised trial of steroid therapy in acute liver failure. *Gut* 1979; 20:620–623
 101. Munoz SJ, Moritz MJ, Martin P, et al: Relationship between cerebral perfusion pressure and systemic hemodynamics in fulminant hepatic failure. *Transplant Proc* 1993; 25:1776–1778
 102. Ling GS, Neal CJ: Maintaining cerebral perfusion pressure is a worthy clinical goal. *Neurocrit Care* 2005; 2:75–81
 103. Davies MH, Mutimer D, Lowes J, et al: Recovery despite impaired cerebral perfusion in fulminant hepatic failure. *Lancet* 1994; 343:1329–1330
 104. Marshall LF, Smith RW, Rauscher LA, et al: Mannitol dose requirements in brain-injured patients. *J Neurosurg* 1978; 48: 169–172
 105. Canalese J, Gimson AE, Davis C, et al: Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. *Gut* 1982; 23:625–629
 106. Garcia-Morales EJ, Cariappa R, Parvin CA,

- et al: Osmole gap in neurologic-neurosurgical intensive care unit: Its normal value, calculation, and relationship with mannitol serum concentrations. *Crit Care Med* 2004; 32:986–991
107. Harutjunyan L, Holz C, Rieger A, et al: Efficiency of 7.2% hypertonic saline hydroxyethyl starch 200/0.5 versus mannitol 15% in the treatment of increased intracranial pressure in neurosurgical patients—a randomized clinical trial [ISRCTN62699180]. *Crit Care Med* 2005; 9:R530–R540
 108. Battison C, Andrews PJ, Graham C, et al: Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. *Crit Care Med* 2005; 33:196–202
 109. Ware ML, Nemani VM, Meeker M, et al: Effects of 23.4% sodium chloride solution in reducing intracranial pressure in patients with traumatic brain injury: A preliminary study. *Neurosurgery* 2005; 57:727–736
 110. Munar F, Ferrer AM, de Nadal M, et al: Cerebral hemodynamic effects of 7.2% hypertonic saline in patients with head injury and raised intracranial pressure. *J Neurotrauma* 2000; 17:41–51
 111. Horn P, Munch E, Vajkoczy P, et al: Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. *Neurol Res* 1999; 21:758–764
 112. Murphy N, Auzinger G, Bernel W, et al: The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. *Hepatology* 2004; 39:464–470
 113. Jalan R, Olde Damink SW, Deutz NE, et al: Moderate hypothermia in patients with acute liver failure and uncontrolled intracranial hypertension. *Gastroenterology* 2004; 127:1338–1346
 114. Jalan R, Olde Damink SW, Deutz NE, et al: Moderate hypothermia prevents cerebral hyperemia and increase in intracranial pressure in patients undergoing liver transplantation for acute liver failure. *Transplantation* 2003; 75:2034–2039
 115. Forbes A, Alexander GJ, O'Grady JG, et al: Thiopental infusion in the treatment of intracranial hypertension complicating fulminant hepatic failure. *Hepatology* 1989; 10:306–310
 116. Clemmesen JO, Hansen BA, Larsen FS: Indomethacin normalizes intracranial pressure in acute liver failure: A twenty-three-year-old woman treated with indomethacin. *Hepatology* 1997; 26:1423–1425
 117. Tofteng F, Larsen FS: The effect of indomethacin on intracranial pressure, cerebral perfusion, and extracellular lactate and glutamate concentrations in patients with fulminant hepatic failure. *J Cereb Blood Flow Metab* 2004; 24:798–804
 118. Trewby PN, Warren R, Contini S, et al: Incidence and pathophysiology of pulmonary edema in fulminant hepatic failure. *Gastroenterology* 1978; 74(5 Pt 1):859–865
 119. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308
 120. Gajic O, Dara SI, Mendez JL, et al: Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 2004; 32:1817–1824
 121. Bonnet F, Richard C, Glaser P, et al: Changes in hepatic flow induced by continuous positive pressure ventilation in critically ill patients. *Crit Care Med* 1982; 10:703–705
 122. McGuire G, Crossley D, Richards J, et al: Effects of varying levels of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure. *Crit Care Med* 1997; 25:1059–1062
 123. Shah MR, Hasselblad V, Stevenson LW, et al: Impact of the pulmonary artery catheter in critically ill patients: Meta-analysis of randomized clinical trials. *JAMA* 2005; 294:1664–1670
 124. Mehta RL: Indications for dialysis in the ICU: Renal replacement vs. renal support. *Blood Purif* 2001; 19:227–232
 125. Davenport A, Will EJ, Davison AM: Early changes in intracranial pressure during haemofiltration treatment in patients with grade 4 hepatic encephalopathy and acute oliguric renal failure. *Nephrol Dial Transplant* 1990; 5:192–198
 126. Mehta RL: Continuous renal replacement therapy in the critically ill patient. *Kidney Int* 2005; 67:781–795
 127. Davenport A, Will EJ, Davidson AM: Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. *Crit Care Med* 1993; 21:328–338
 128. Swamy AP, Cestero RV: Mannitol and maintenance hemodialysis. *Artif Organs* 1979; 3:116–119
 129. Detry O, Arkadopoulos N, Ting P, et al: Intracranial pressure during liver transplantation for fulminant hepatic failure. *Transplantation* 1999; 67:767–770
 130. Keays R, Potter D, O'Grady J, et al: Intracranial and cerebral perfusion pressure changes before, during, and immediately after orthotopic liver transplantation for fulminant hepatic failure. *Q J Med* 1991; 79:425–433
 131. Daas M, Plevak DJ, Wijdicks EF, et al: Acute liver failure: Results of a 5-year clinical protocol. *Liver Transpl Surg* 1995; 1:210–219
 132. Bismuth H, Samuel D, Castaing D, et al: Liver transplantation in Europe for patients with acute liver failure. *Semin Liver Dis* 1996; 16:415–425
 133. Trotter JF, Blei AT, Everhart JE, et al: Outcomes of donors and recipients following living donor liver transplantation for acute liver failure. *Abstr. Hepatology* 2006; 44:
 134. Ejlersen E, Larsen FS, Pott F, et al: Hepatectomy corrects cerebral hyperperfusion in fulminant hepatic failure. *Transplant Proc* 1994; 26:1794–1795
 135. Chugh KS, Sakhuja V, Gupta KL, et al: Renal mucormycosis: Computerized tomographic findings and their diagnostic significance. *Am J Kidney Dis* 1993; 22:393–397
 136. Ringe B, Lubbe N, Kuse E, et al: Total hepatectomy and liver transplantation as two-stage procedure. *Ann Surg* 1993; 218:3–9

APPENDIX

Acute Liver Failure Study Group. Members and institutions participating in the Acute Liver Failure Study Group: W.M. Lee, MD (principal investigator), Julie Polson, MD, and Carla Pezzia, University of Texas Southwestern, Dallas, TX; Anne Larson, MD, University of Washington, Seattle, WA; Timothy Davern, MD, University of California, San Francisco, CA; Paul Martin, MD, Mount Sinai School of Medicine, New York, NY; Timothy McCashland, MD, University of Nebraska, Omaha, NE; J. Eileen Hay, MD, Mayo Clinic, Rochester, MN; Natalie Murray, MD, Baylor University Medical Center, Fort Worth, TX; A. Obaid S. Shaikh, MD, University of Pittsburgh, Pittsburgh, PA; Andres Blei, MD, Northwestern University, Chicago, IL; Atif Zaman, MD, University of Oregon, Portland, OR; Steven Han, MD, University of California, Los Angeles, CA; Robert Fontana, MD, University of Michigan, Ann Arbor, MI; Brendan McGuire, MD, University of Alabama, Birmingham, AL; Ray Chung, MD, Massachusetts General Hospital, Boston, MA; Alastair Smith, MB, ChB, Duke University Medical Center, Durham, NC; Michael Schilsky, MD, Cornell/Columbia University, New York, NY; Adrian Reuben, MBBS, Medical University of South Carolina, Charleston, SC; Santiago Munoz, MD, Albert Einstein Medical Center, Philadelphia, PA; Rajender Reddy, MD, University of Pennsylvania, Philadelphia, PA; R. Todd Stravitz, MD, Virginia Commonwealth University, Richmond, VA; Lorenzo Rossaro, MD, University of California at Davis, Sacramento, CA; Raj Satyanarayana, MD, Mayo Clinic, Jacksonville, FL; and Tarek Hassanein, MD, University of California, San Diego, CA.